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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,066	RAITANO ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-58* is/are pending in the application.

4a) Of the above claim(s) *51-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04/08/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of group I, claims 44-50, in Paper of 01/29/04 is acknowledged and entered.

Claims 44-58 are pending in the instant application and Claims 51-58 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group I, Claims 44-50 are currently under prosecution.

INTERFERENCE REMARKS

In a communication of 12/14/01, Applicant remarks that the Office may wish to consider the possibility of interference with co-pending applications related to WO 00/20590, such as 09/167219.

It is noted that an interference with co-pending applications would be considered only when the claims of the instant application are in the allowable forms.

CONTINUATION DATA

The continuation data have been updated as follows:

This application is a divisional application of U.S. Serial No. 09/680,728, filed 5 October 2000, and now pending, which claims priority from U.S. Provisional Patent Application No. 60/157,902, filed 5 October 1999, now abandoned. The contents of these applications are incoporated herein by reference.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, DEPOSIT REQUIREMENT

Claim 46 is rejected under 35 USC 112, first paragraph.

Claim 46 is drawn to a recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein any amino acid substitution are conservative substitutions, and wherein the polypeptide is encoded by the cDNA contained in plasmid p101P3A11, deposited with American Type Culture Collection (ATCC) as accession No.PTA-312.

The specification discloses that the sequence of a polynucleotide encoding a PHOR-1 polypeptide is encoded by the cDNA contained in plasmid p101P3A11, deposited with American Type Culture Collection (ATCC) on July 2, 1999, as accession No.PTA-312.

The specification is objected to under 35 USC 112, first paragraph, as failing to provide an enabling disclosure and failing to provide an adequate description of the claimed invention without evidence that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

Although the specification provides the name and accession number of the plasmid, and the name of the depositor, where the cells are deposited, the date of the deposition, the specification fails to provide an adequate description of the claimed invention, e.g .the address of the depositor.

Moreover, applicant is required to submit an affidavit or declaration stating that all restrictions upon public access to the deposits will be irrevocably removed upon the granting of a patent on this application, and that the deposit will be replaced if viable samples cannot be dispensed by the depository.

The identifying information set forth in 37 CFR 1.809(d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Claim 46 is rejected under USC 112, first paragraph, for the reasons set forth in the objection to the specification.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

Claims 44, 47-50 are rejected under 35 USC 112, first paragraph.

Claims 44, 47-50 are drawn to:

a) A recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein any amino acid substitution are conservative substitutions (Claim

44). Said nucleic acid further comprises control sequences to effect production of said PHOR-1 polypeptide (Claim 47).

b) Recombinant cells modified to contain the nucleic acid of claim 47 (Claim 48), and

c) A method for producing a PHOR-1 polypeptide (Claims 49-50).

The specification discloses that embodiments of the instant invention include a wide variety of variants of PHOR-1 proteins, such as polypeptides having amino acid insertions, deletions and substitutions, and that said variants could be made using methods known in the art (p.28, lines 20-24).

Claims 44, 47-50 encompass a recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein any amino acid substitution are conservative substitutions; however, said amino acid sequence could have any deletion and/or insertion with any amino acid, at any position throughout the entire length of the amino acid.

Further, it is noted that the language a method to produce "a PHOR-1 polypeptide" of claims 49-50 encompasses a method for producing variants of SEQ ID NO:2, because a PHOR-1 polypeptide includes variants of SEQ ID NO:2, as defined in the specification, on page 18, first paragraph, which recites that the PHOR-1 gene or protein is meant to include other PHOR-1 proteins and variants that share at least 50%, or 60% or 70% amino acid homology.

In other words, the claims 44, 47-50 encompass a recombinant nucleic acid encoding a variant of the polypeptide of SEQ ID NO:2, with unknown

structure and function, and a method to produce a variant of the polypeptide of SEQ ID NO:2.

The findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are clearly relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, per Lilly by structurally describing a representative number of nucleic acids encoding polypeptides at least 90% identical to the

polypeptide of SEQ ID NO:2, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2 required to practice the claims 44, 47-50 in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, other than SEQ ID NO:1, nor does the specification provide any partial common structure of such nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, nor any physical or chemical characteristics of a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, other than SEQ ID NO:1, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses a single polynucleotide encoding the polypeptide of SEQ ID NO:2, i.e. SEQ ID NO:1, this does not provide a description of a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2 that would satisfy the standard set out in Enzo.

The specification also fails to describe a a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2 by the test set out in Lilly. The specification describes only a single polynucleotide encoding the polypeptide of SEQ ID NO:2, i.e. SEQ ID NO:1. Therefore, it necessarily fails to describe a "representative number" of such species. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, that is required to practice the claimed invention. Further, since the specification does not provide an adequate written description of a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, the specification also does not provide an adequate written description of a method of producing a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2 or a variant of the polypeptide of SEQ ID NO:2.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE

1. Claims 44, 47-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide sequence shown in SEQ ID NO:1, or a polynucleotide sequence encoding SEQ ID NO:2, **does not reasonably provide enablement for a nucleic acid encoding a polypeptide at least 90% identical to the polypeptide of SEQ ID NO:2, wherein any amino acid substitutions are conservative substitution.** The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 44, 47-50 are drawn to:

a) A recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein any amino acid substitution are conservative substitutions (Claim 44). Said nucleic acid further comprises control sequences to effect production of said PHOR-1 polypeptide (Claim 47).

b) Recombinant cells modified to contain the nucleic acid of claim 47 (Claim 48),

and

c) A method for producing a PHOR-1 polypeptide (Claims 49-50).

Claims 44, 47-50 encompass a recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein any amino acid substitution are conservative substitutions; however, said amino acid sequence could have any deletion and/or insertion with any amino acid, at any position throughout the entire length of the amino acid.

In other words, the claims 44, 47-50 encompass a recombinant nucleic acid encoding a variant of the polypeptide of SEQ ID NO:2, with unknown structure and function.

Further, it is noted that the language a method to produce "a PHOR-1 polypeptide" of claims 49-50 encompasses a method for producing variants of SEQ ID NO:2, because a PHOR-1 polypeptide includes variants of SEQ ID NO:2, as defined in the specification, on page 18, first paragraph, which recites that the PHOR-1 gene or protein is meant to include other PHOR-1 proteins and variants that share at least 50%, or 60% or 70% amino acid homology.

Applicants have not shown how to make and use the claimed variants which are capable of functioning or have the properties of the polynucleotide of SEQ ID NO:1, as that which is being disclosed.

The claims read on a variant nucleotide sequence encoding a variant of the polypeptide encoded by SEQ ID NO:1, wherein said variant has any type of deletion and insertion, at any amino acid, throughout the length of the polypeptide, as long as the resultant amino acid sequence is at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2). The specification and the claims do not place any limit on which amino acid to be subjected to deletion and/or insertion, nor the type of amino acids replacing the original amino acids. Thus the scope of the claims includes nucleotide sequences encoding numerous structural variants. Although the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which amino acids could be deleted or inserted in the encoded polypeptide, so that the claimed polynucleotide and the encoded polypeptide could function as contemplated.

One cannot extrapolate the teaching in the specification to the scope of the claims because one cannot predict that the claimed variants of SEQ ID NO:1 encoding variants of the polypeptide of SEQ ID NO:2 would have properties related to that of SEQ ID NO:1. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology and that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at

position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

The specification does not disclose how to make the claimed nucleic acid molecules, such that they would function or have the properties as claimed, or how to use said nucleic acid molecules if they did not have the function or properties claimed.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification

would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability that the claimed variants would have the property or function of SEQ ID NO:1 , the lack of adequate disclosure in the specification on how to make such variants, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

2. If Applicant could overcome the above 112, first paragraph rejection, Claim 48 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell comprising the polynucleotide of SEQ ID NO:1, and control sequences to effect production of the polypeptide of SEQ ID NO:2, **does not reasonably provide enablement for "a recombinant host cell"** modified to contain the recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein any amino acid substitution are conservative substitutions, and control sequences to effect production of said PHOR-1 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claim 48 is drawn to "a recombinant host cell" modified to contain the recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2) over its entire length, wherein

any amino acid substitution are conservative substitutions, and control sequences to effect production of said PHOR-1 polypeptide.

The specification discloses that using expression vector such as retroviral vector, PHOR-1 may be preferably expressed in several prostate cancer (p.25, lines 16-23). The specification contemplates gene therapy (p. 56-57) and viral gene delivery system to deliver a PHOR-1-encoding nucleic acid molecule as cancer vaccines (p.58)

It is noted that although there is definition of a recombinant DNA, which is a DNA molecule that has been subjected to molecular manipulation in vitro (p.25, first paragraph), there is no definition of a recombinant host cell.

In view of a lack of a definition of a recombinant host cell, one could reasonably interpret that a recombinant host cell encompasses a host cell in vivo that comprises a recombinant nucleic acid encoding a polypeptide at least 90% identical to the amino acid sequence of PHOR-1 (SEQ ID NO:2), for cancer gene therapy as contemplated.

One cannot extrapolate the teaching in the specification to the scope of the claim for the following reasons: The state of the gene therapy art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be

advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus in view of the teaching in the art and in the specification, one cannot predict that in vivo host cell comprising the claimed polynucleotide could be produced from cancer therapy as contemplated.

Thus in view of the teaching in the art that gene therapy is unpredictable, and the lack of disclosure of any objective evidence concerning obtaining in vivo host cell transfected with the claimed polynucleotide, it would be undue experimentation for one of skill in the art to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

PATENT EXAMINER

February 15, 2004